BASIC RESEARCH STUDIES

From the Western Vascular Society

Thin-film nitinol (NiTi): A feasibility study for a novel aortic stent graft material

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Objective: **Although technological improvements continue to advance the designs of aortic stent grafts, miniaturization of the required delivery systems would allow their application to be available to a wider range of patients and potentially decrease the access difficulties that are encountered. We performed this feasibility study to determine if thin-film NiTi (Nitinol) could be used as a covering for stent grafts ranging from 16 mm to 40 mm in diameter. Specifically, we wished to determine the profile reduction attainable and improve the flexibility of our design.**

Methods: **Using a novel hot-sputter deposition technique, we created sheets of thin-film NiTi (TFN) with a tensile strength of >500 Megapascal (MPa) and thickness of 5-10 microns. TFN was used to cover stents, which were then deployed in vitro. Patterned thin film was fabricated via a lift-off technique; grafts were constructed with stents ranging from 16-40 mm and deployed in a pulsatile flow system from the smallest diameter polymer tubing into which the stent and TFN would fit. The bending/stiffness ratio vs similar sized expanded polytetrafluoroethylene (ePTFE)-covered stents was also determined.**

Results: **TFN was created in both non-patterned and patterned forms, with a tensile strength of >100 MPa for the latter. We created devices that were successfully deployed via delivery systems half the size of fabric-covered stent grafts (ie, the 16 mm stent graft that originally was delivered via a 16French (F) system was reduced to 8F, and the 40 mm stent graft delivered via a 24F system was reduced to 12F). No migration of the devices was observed with deployment in both straight and curved tubing, which was sized so that the stent grafts were oversized by 20%. Both forms of the thin-film were noted to be more flexible than the same sized ePTFE stent graft, and the patterned graft had an additional 15-30% flexibility vs the non-patterned film.**

Conclusion: **These in vitro results demonstrate the feasibility of TFN for covering stent grafts designed for placement in the aorta. The delivery profile can be significantly reduced across a wide range of sizes, while the material remained more flexible than ePTFE. (J Vasc Surg 2009;50:375-80.)**

Clinical Relevance: **This article describes a basic science/engineering project with clear implications for clinical application of an aortic endograft. Our continuing projects along these lines will be reported as these data become available. The clinical relevance is also addressed within the body of the manuscript, particularly in the discussion.**

Since the introduction of covered stents, there has been rapid application of these devices for a variety of clinical situations. Parodi's description of abdominal aortic aneurysm (AAA) repair using a stent graft was followed by the diffusion of a variety of commercially available products into the vascular surgeons' armamentarium, and these stent grafts are now used routinely for the treatment of both AAAs and thoracic aneurysms.[1,2] One of the factors that currently limits the utilization of these grafts, particularly with thoracic endovascular aneurysm repair (TEVAR), is their large caliber and long delivery systems, which can be up to 25 French (F) (8.3 mm) for a 46 mm thoracic endograft. Insertion of large delivery catheters can make the arterial access and tracking through small, tortuous, or calcified vessels difficult or impossible.

There have been considerable attempts to miniaturize the pre-deployment diameter of aortic stent grafts and their delivery components. Currently available aortic stent grafts are constructed using a combination of a metallic stent, usually stainless steel, or an alloy such as nitinol (NiTi) with a covering made of either a woven polyester fabric (such as the Cook Zenith grafts, Cook Inc, Indianapolis, Ind) or expanded polytetrafluoroethylene (ePTFE) as with W.L. Gore & Associates (Flagstaff, Ariz) TAG and Excluder devices. The major determinant of the diameter of these devices is the covering (ie, 50% of catheter space is occupied by the ePTFE covering), and not the stent itself. Thus,

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Competition of interest: none.

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reducing the thickness of the covering provides a strategy for reducing the diameter of the entire delivery system.

Our laboratory has been exploring the feasibility of using thin-film NiTi (TFN) as a novel covering for aortic stent grafts, to reduce the delivery system diameter. Utilizing a novel hot target sputter deposition process, we have created corrosive-resistant TFN with a thickness as small as 1 micron to a thickness as large as 15 microns and from it fashioned a variety of devices.[3,4] The biocorrosive and fatigue properties of thin-film NiTi have been cursorily evaluated in previous studies. These data showed the TFN to be more corrosion resistant than either bulk NiTi or 316L stainless steel and the TFN did not undergo any degradation during a one million cycle pulsatile flow test under 115 mm Hg systolic blood pressure.[5] Based on these data from our laboratory, we do not expect fatigue degradation of the TFN material (ie, load and strain levels in covered stent smaller than heart valve) or significant corrosion of the TFN (ie, less corrosive than existing stents on the market).

TFN has many advantageous qualities including: (1) a long and safe history of human implantation in the form of numerous types of devices in multiple anatomic locations; (2) superelastic qualities which allow it to undergo a stress-induced phase transformation (elastically recoverable strain of 10%); (3) shape memory properties which provide easy deformation in the martensite phase at a low temperature and shape recovery in the austenite phase at elevated temperature (eg, body temperature); and (4) a tensile strength of greater than 500 Megapascal (MPa).[6] These properties suggest TFN has potential as a covering for the larger sized stent grafts required to treat aneurysms of the aorta while dramatically reducing the required thickness of the stent covering. In addition to material properties advantages, TFN-covered stents are expected to be comparable in terms of cost to ePTFE devices, where the majority of the cost is associated with attachment issues (ie, hand sewing) rather than the material costs of NiTi. This current feasibility study set out to address the following related questions: (1) can we construct TFN stent grafts of larger sizes (16-40 mm) and successfully deploy them in vitro; (2) can we provide these stent grafts with the necessary pre-deployment flexibility required to navigate tortuous vessels during the delivery process and to conform to the aorta following deployment; and (3) can we reduce the diameter of the stent graft deployment system?

METHODS

Thin-film NiTi creation. Films were deposited on a 4" silicon wafer buffered with a 500 nm silicon oxide layer to both retard silicide formation and prevent the film from adhering to the substrate. The bulk NiTi source was bombarded with argon while the substrate was translated in 80 mm sections perpendicular to the sputtering direction. This technique has led to the production of TFN with compositional variation of less than 1 atomic percent.[7] The film was then removed from the substrate and crystallized for 120 minutes at 500°C in a vacuum of less than 1×10^{-7} torr. The film was then micro-machined using lithographic techniques into rectangular sheets and rolled onto 0.64 mm steel cylinders in preparation for insertion into the appropriate delivery catheter. The TFN material used for this study had an austenite finish temperature of approximately 34°C as measured from differential scanning calorimeter (DSC) following deposition and removal from the wafer. The superelastic and shape recovery properties of this film were measured with a mechanical load frame at body temperature and room temperature, respectively.

Stent graft fabrication and in vitro deployment. The TFN-covered stent and delivery system consists of three major components, the stent, TFN, and the catheter. The stent was obtained from a commercially available ePTFE-covered thoracic stent. The ePTFE was subsequently removed from the thoracic stent. The TFN sheets were sized to provide full coverage of the deployed thoracic stent. A polymer catheter was used for delivery, and we used the smallest diameter tubing into which both the bare stent and the TFN would fit without deforming either structure. The TFN material was mechanically constrained and inserted in the delivery catheter. Following this, the thoracic stent was mechanically constrained and inserted into the delivery catheter. In this process, the TFN is not mechanically attached to the thoracic stent, but in future models this will be revised. Also, in this scenario, the TFN is on the vessel side of the stent. Placing the film on the lumen side would require mechanical fixation which should be relatively easy to achieve. Once in the delivery catheter, the mechanical constraint was removed (ie, the film partially deployed in the catheter). The diameters of the actual delivered devices ranged from 16-40 mm. To determine the minimum size deployment catheter the stent graft could be inserted into, successively smaller sizes were tested for each stent, and the tubing with the smallest diameter into which the bare stent would fit was used for the subsequent stent graft delivery.

These stent graft constructs were deployed from the polymer catheter with a push-wire system into polyvinyl chloride (PVC) tubing (ie, simulating the vascular curvature) with a range of diameters (12-44 mm). Flow was provided in the PVC tubing via a Harvard Apparatus pulsatile pump (Harvard Medical, Hollison, Mass) with a systole/diastole ratio of 40:60 and a stroke volume of 10-30 cc per stroke (600-2400 cc/minute) to evaluate for in vitro migration of our stent grafts under pulsatile conditions.

Micromachined patterns through thin-film NiTi. In addition to evaluating thin-film NiTi-covered stents, we also investigated the use of patterned NiTi film. Patterned NiTi film contains small diameter holes increasing the flexibility of the material and is analogous to a woven fabric. We hypothesized that the patterned film would dramatically reduce the bending stiffness of the stent/delivery system when compared to non-patterned film and also allow for better conformability to the target blood vessel. Using a lift-off method and photolithography, holes as small as 20 microns and as large as 70 microns were

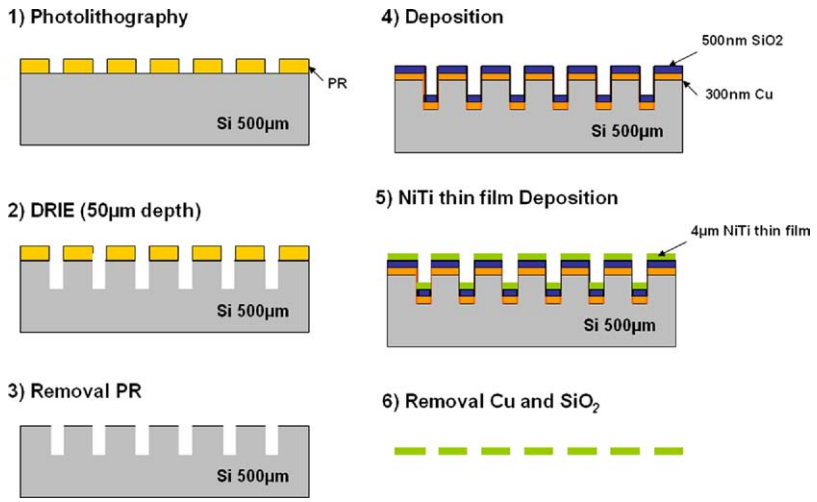

Fig 1. The lift-off process used to fabricate patterns on thin film nitinol (NiTi) is displayed above schematically. See text for details. *DRIE,* Deep reactive ion etching; *PR,* photoresist; *Cu,* copper; *SiO_2,* silicon dioxide.

Table. Delivery catheter size changes as a function of graft material

Original stent graft diameter	*Original stent graft delivery system diameter*	*Delivery catheter for bare stent*	*Delivery catheter for thin-film NiTi stent graft*
16 mm	16F	7F	8F
20 mm	18F	8F	9F
26 mm	20F	10F	10F
37 mm	24F	11F	12F
40 mm	24F	11F	12F

NiTi, Nitinol; *F,* French.

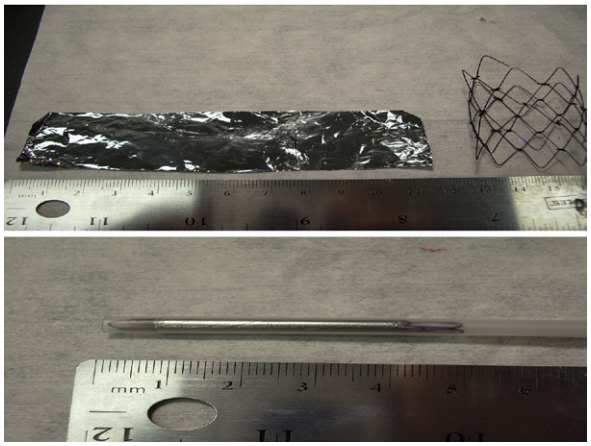

Fig 2. Bare metal stent and thin-film nitinol (NiTi) before assembly **(A)**. This 37-mm stent graft is also shown collapsed inside a 12F delivery catheter **(B)**.

investigated. The first step in the lift-off method for producing patterned TFN is to create 50 micron deep trenches using photolithography and a deep reactive ion etching (DRIE) technique (Fig 1). Following this, a 500 nm copper (Cu) sacrificial layer and a 500 nm silicon dioxide

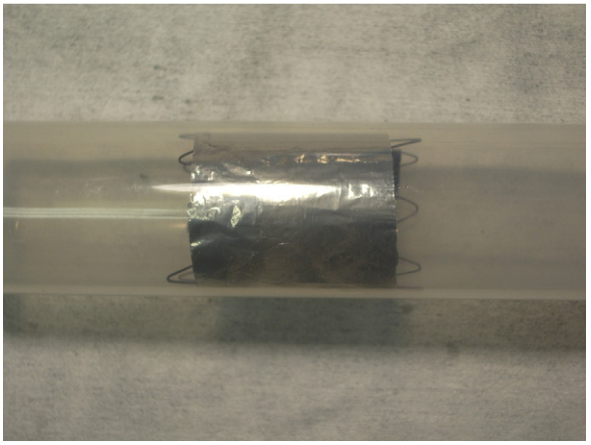

Fig 3. Displayed in longitudinal view is a 37-mm thin-film nitinol (NiTi)-covered stent graft uniformly deployed in a 30 mm pulsatile flow circuit following placement via a 12F delivery catheter.

(SiO_2) barrier layer are deposited by e-beam evaporation and plasma-enhanced chemical vapor deposition (PECVD) techniques, respectively. The TFN is deposited by direct current sputtering process onto the SiO_2. Cu and SiO_2 layers are removed and stand-alone film is crystallized at 500°C for 120 minutes in a vacuum of less than 1×10^{-7} torr.

RESULTS

Preliminary work with the commercial stent grafts was performed, and we determined that stents were easily collapsed and re-inserted into delivery tubing half the diameter of the original system less one French size. The addition of TFN-covering onto the stents allowed the stent graft combinations to be fitted into delivery catheters half the original diameter; that is, the thin-film covering led to one additional French size (Table) (Fig 2). One stent was used for

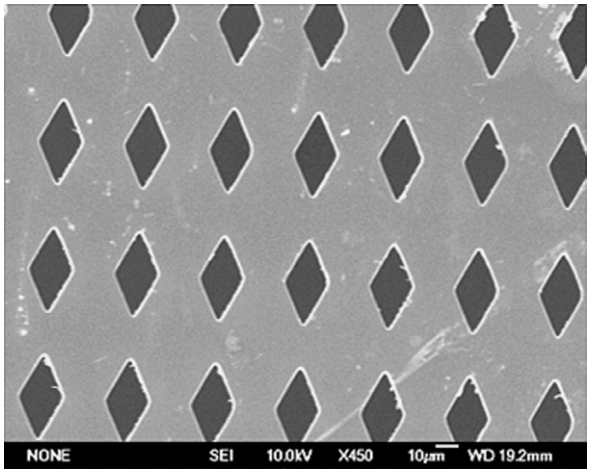

Fig 4. Scanning electron micrograph image of patterned thin-film nitinol (NiTi) demonstrating uniform, diamond-patterned holes.

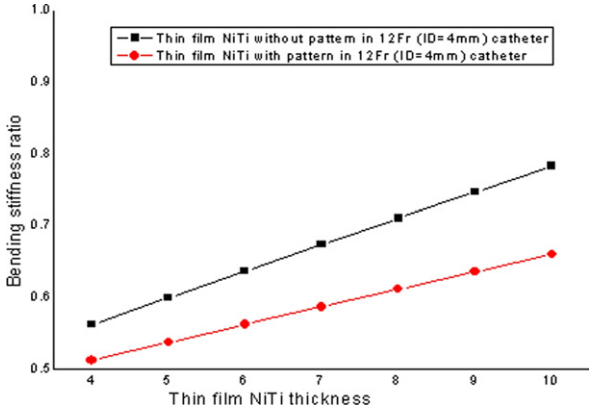

Fig 5. A plot of the bending stiffness ratio of TFN vs ePTFE where a ratio of 0.5 indicates that TFN is half the bending stiffness of expanded polytetrafluoroethylene (ePTFE) (ie, more compliant). In this case, patterned thin-film nitinol (TFN) (*red line*) is compared to non-patterned TFN (*black line*). *NiTi,* Nitinol; *Fr,* French.

each of the tests shown in the Table, in order to evaluate how delivery catheter size changes as a function of graft material (ie, from ePTFE to TFN). There was no observed structural damage to either the stents or the TFN at these diameters, and the stents were then successfully deployed in our pulsatile circuit in tubing for which the stent grafts were oversized by 20% (Fig 3). Migration of the stent graft combination was not observed at any pulsatile conditions measured up to a flow rate of 47 cc/second (pressure of 500 mm Hg). Furthermore, these in vitro deployment tests used the same sheaths for femoral access and there was no significant kinking or lack of pushability with no added reinforcement necessary for the delivery system.

The TFN contained holes that were diamond-shaped with dimensions of 20 × 10 microns, 40 × 20 microns, and 60 × 30 microns. Fig 4 shows a scanning electron microscope (SEM) image of the 5-micron-thick patterned TFN. As can be seen from the photograph, the patterning is uniform. The in vitro tests of insertion of TFN-covered stents in the delivery catheter and deployment were performed 20 times per TFN-covered stent. No damage or failure was observed as the force needed to push the device out of the delivery catheter was quite small compared to the high tensile strength (greater than 100 MPa) of TFN. For this particular film, the holes were diamond-shaped and approximately 20 microns along the longest axis and 10 microns along the shortest axis. Note that the NiTi edges are clean and smooth and do not contain undercutting as is observed in most wet etching techniques. The SEM also clearly shows that the hole registrations are uniform and equally spaced throughout the film. These features allow the patterned TFN sheets to be deformed without adverse effects on subsequent stent graft deployment. The stent grafts with the patterned coverings were then deployed in curved tubing with a radius of curvature of 0.2 m under pulsatile conditions. Again, no migration was observed. Stent grafts were then removed from the in vitro system. Analysis of the thin film demonstrated no structural damage.

Calculations were performed to determine the bending stiffness of the patterned thin film vs the non-patterned product. This was used as a surrogate for determining the flexibility of the material. Fig 5 displays the bending stiffness ratio for the two materials over a range of increasing thickness for the film in the pre-deployment configuration for a 12F delivery system. The scale is set so that a ratio of 1 is equal to that for an ePTFE-covered stent graft of the same dimensions. Both forms of the TFN have increased flexibility relative to the ePTFE stent graft, and there was a 15-30% increase in flexibility across the scale for the patterned thin film vs the non-patterned form. In general, lower bending stiffness is desirable to increase the trackability of the delivery system. Therefore, the film should be as thin as possible. Using the strength properties of TFN (500 MPa) and the strength properties for ePTFE (~1 MPa), the thickness of TFN could be $1/500^{th}$ the value of ePTFE (ie, ~0.5 μm) and be effectively as strong as ePTFE. This suggests all the thicknesses considered in Fig 5 are substantially stronger than current ePTFE stent structures.

DISCUSSION

These results demonstrate in vitro the feasibility of using TFN for the construction of aortic stent grafts with the benefit of reducing the diameter of the delivery systems for these devices. The systems for a variety of commercially available stent grafts were reduced by what is clearly a clinically relevant degree (half of the original delivery system). To be fair, we do not have a finished prototype of this novel covered stent and anticipate that fastening the stent to the thin film and adding a bifurcated stent graft may add to the profile. However, the dramatic reduction of the space occupied by the thin-film NiTi covering is clear, with

the thin film itself adding a thickness of only 1F. Furthermore, the many design and engineering facets needed for a bifurcated AAA graft are not issues with regards to TEVAR, where access issues due to the size of the graft and delivery system limit their use. This raises the possibility that development of lower profile stents could lead to even smaller systems than described in this document. That is, with previous coverings there was little impetus to miniaturize the stent, as the bulk of the diameter derived from the covering itself. We have also demonstrated that our lift-off method represents an acceptable fabrication process to produce TFN with sufficient flexibility of both the predeployment construct and the deployed stent graft, at least in an in vitro setting for stent grafts >16 mm in diameter.

NiTi is currently used routinely for many implantable devices, and there have been few issues with biocompatibility. There are some concerns regarding the release of nickel, although the clinical significance of these findings is not known.[5] There is a body of literature regarding the response of endothelial cells and vascular smooth muscle cells to NiTi surfaces. Both cell types appear to attach to the thin films and undergo cell division in vitro.[8] There are a variety of modifications of the thin-film surface (for example, surface roughness) that also impacts on the characteristics of vascular cells when exposed to these surfaces. However, it should be pointed out that the surface roughness of thin-film NiTi (ie, 5 nm) is an order of magnitude smaller than surface roughness of commercially available NiTi stents (ie, 500 nm). With regards to thrombogenicity, the data are unclear. Comparisons to stainless steel in vitro have led to conflicting results,[9,10] although in vivo work from our laboratory suggests favorable characteristics.[11] In addition to the chemical properties of the thin-film NiTi, the impact of the mechanical configuration of the patterned thin film on the biological response to the material also needs to be evaluated, as it may be different than that of the continuous thin-film NiTi sheets. This is an area of ongoing investigation in our laboratory.

In this study, endotension, permeability, and ultrafiltration characteristics through the patterned holes was not evaluated. Given that platelets and red blood cells are on the order of 5-10 μm, the hole sizes used in this study may allow leakage. However, standard lithography is capable of 2 μm size features and e-beam lithography is capable of 0.1 μm features. These small sizes would prevent leakage and will be evaluated in future experiments. However, the tensile strength of the thin-film NiTi itself is known to be orders of magnitude stronger than ePTFE.

In addition to reducing the profile of larger stent grafts, there are several other potential benefits of using thin-film NiTi. One is a possible advantage with regards to infection resistance. Although NiTi can become infected, this risk, at least in other anatomic locations, is much less than that with woven polyesters or ePTFE.[12] We are currently evaluating the ability of the material to withstand infection in vitro.

With regards to our particular sputter deposition technique, the main advantages are found in the uniformity of our thin film and the ability to provide thicker deposits (up to 15 μm), which is not possible with other techniques for thin film production such as pulsed laser deposition.[13] The details of the deposition technique become particularly critical when fabricating sheets of thin film for creating larger stent grafts. Our technique is also faster with the concomitant implications for industrial production of these devices. Even at the extremely thin profiles afforded by our thin-film NiTi fabrication, it should be remembered that the tensile strength of NiTi is still several orders of magnitude greater than that afforded by ePTFE or woven polyesters. For example, the tensile strength of ePTFE is roughly 10 MPa, and this number is significantly less when it is in a tubular vs a sheet form. Thus, we can achieve a thickness of our film for medical applications that can be orders of magnitude thinner.

From a clinical standpoint, thoracic aortic aneurysms appear to be the lesions most likely to benefit from these devices for a number of reasons. Most significant among these are the large diameter grafts required at this location. Indeed, two grafts measuring 46 mm are soon to be available in the United States, and these have delivery systems of 24 and 25F diameter.[14] Our current data suggest we could deploy such a device via a 12 or 13F system. In addition to the size itself, there is the issue of navigating these stent grafts the long distance from the femoral or iliac conduit access site where the smaller diameter device would clearly be less difficult to successfully deliver to the thoracic aorta. Another application to arise from an early design from this study is that for a contralateral limb for AAA treatment. For patients with limited iliac access unilaterally, the 16 mm device we created could be delivered via an 8F sheath, while a different 12 mm limb we created can be delivered via a 6F sheath.

The above data support the feasibility of our design for a TFN-covered stent graft in vitro for use in large arteries (treatable by grafts 16 mm and larger). Although the data are all in vitro, several questions regarding fabrication and deployment have been successfully addressed. We are currently investigating the in vivo deployment of our stent grafts in animal models.

A number of issues remain areas of active research, including the fastening of the stent to the TFN, and fashioning devices of more complex design, such as the bifurcated design required for an AAA stent graft. Also, as mentioned above, endotension, permeability, and ultrafiltration characteristics were not tested using the patterned TFN and will need to be evaluated in future studies as these are crucial determinants in developing a successful stent graft. Although the grafts in this study were constructed with the thin film outside of the stent, we have also experimented with designs where the thin film is inside the supportive stent. In addition, there are designs with support wires of NiTi on the outside of the thin film to provide external support to the film if it is not in apposition to an arterial wall, ie, the portion of a large aneurysm between the attachment zones. Finally, it should be pointed out that the thin film itself need not be rolled to form cylinders; it can be preformed and attached to itself or the stent by a variety of

methods currently under investigation in our laboratory. The patterned film in particular can be collapsed easily in the martensite phase with recovery of the desired shape at austenite phase (body temperature). We are also investigating tissue in-growth with our patterned grafts to determine the appropriate size for adequate incorporation of these stent grafts.

AUTHOR CONTRIBUTIONS

Conception and design: DR, YC, KM, GC, PL
Analysis and interpretation: DR, YC, KM, GC, PL
Data collection: DR, AT, YC, KM, GC
Writing the article: DR, AT, PL
Critical revision of the article: DR, AT, YC, GC, PL
Final approval of the article: DR, AT, YC, GC, PL
Statistical analysis: DR, YC, KM, GC
Obtained funding: DR, GC
Overall responsibility: DR, GC

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